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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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GLAXO GROUP LIMITED,

Plaintiff, Civil Action No. 04-171-KAJ

v.

TEVA PHARMACEUTICALS USA, INC. and
TEVA PHARMACEUTICAL INDUSTRIES
LIMITED,

Defendants.
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EXPERT REPORT OF PROFESSOR ARTHUR H. KIBBE

I. My Qualifications

1. I am currently Chair of, and a Tenured Professor in, the Department of Pharmaceutical Sciences at Wilkes University. My complete *curriculum vitae* and a list of publications I have authored are attached hereto as Exhibit A. A list of the documents I have considered in forming my opinion are attached hereto as Exhibit B.

2. I received my B.S. in Pharmacy in 1966 from Columbia University in New York City and received both my M.S. and Ph.D. in Pharmacy from the University of Florida in 1968 and 1973, respectively. My Ph.D. includes a specialty in Formulation Design, Pharmacokinetics and Biopharmaceutics.

3. I am a Fellow of the Academy of Pharmaceutical Research and Science, and a member of Rho Chi Honorary Pharmaceutical Society. I also have been a Member of the Food and Drug Administration's Scientific Advisory Committee from spring of 2001 to fall 2005 and chairman of that committee from 2002 to 2005. I was also a member of the FDA Scientific Advisory Committee's subcommittee on current Good

alcohol and isopropanol makes them a great choice if you need to easily remove the solvent such as during a film coating process. Propylene glycol and sorbitol on the other hand are used in films as a plasticizer since they have a relatively low vapor pressure.

81. The relative viscosities of each are such that alcohol or isopropanol will thin a mixture while propylene glycol and sorbitol will thicken it. Propylene glycol and sorbitol are sweet to the taste like glycerin or sugar solutions. Alcohol is a CNS depressant and will often potentiate the CNS depressant effects of active ingredients. Isopropanol is toxic orally.

82. It is clear from the above that a person of ordinary skill in the art of pharmaceutical formulation would not expect that propylene glycol could be expected to impart to any mixture the same characteristic as ethanol. It is more likely that sorbitol would be a better substitute for propylene glycol. It is also more likely that isopropanol would work more like ethanol in topical mixtures and is only limited in its use in oral solutions by its known toxicity and not by its physical and chemical characteristics.

83. Both ethanol and propylene glycol are on the GRAS list but this does not mean that they are equivalent for purposes of this invention. The GRAS list is merely a list of pharmaceutical excipients that are acceptable to the FDA.

B. Propylene glycol and ethanol function differently in a ranitidine oral solution and produce different degradation products of the paraben preservatives.

84. Prior to October 1985, the proposed ranitidine syrup formulations relied upon combinations of alkyl *para*-hydroxybenzoate esters (e.g., methyl, propyl and butyl parabens) as preservatives. These formulations did not contain ethanol, but did contain small amounts of propylene glycol as a component of the flavoring. However, the paraben concentration in the syrup degraded at a higher than expected rate, primarily by

hydrolysis, but also by transesterification of the esters with propylene glycol. The impurities generated by transesterification with propylene glycol are 4-hydroxybenzoic acid 2-hydroxy propyl ester or 4-hydroxybenzoic acid 2-hydroxy 2-methyl ester. The effects of these impurities on a patient are unknown.

85. Glaxo eventually determined that a preservative system including only alkyl *para*-hydroxybenzoate esters was insufficient. The ranitidine syrup was reformulated with a preservative system including both alkyl *para*-hydroxybenzoate esters and 7.5% ethanol. The potential degradation product of ethanol transesterification of the propyl or butyl hydroxybenzoate esters used in the new formulation is ethyl *para*-hydroxybenzoate ester, another alkyl *para*-hydroxybenzoate ester. Ethyl *para*-hydroxybenzoate ester is generally recognized as safe.

86. I understand that an equivalent in the patent laws may be defined as something that performs substantially the same function in substantially the same way to achieve the same result as the claimed element. In my opinion, propylene glycol cannot be an equivalent to ethanol under this definition because the '249 patent does not teach the "way" in which the surprising stabilization is accomplished. The '249 patent also does not provide clear guidance of what is considered a "surprising" amount of stabilization, i.e., the result sought. Without this guidance from the '249 patent, it is my opinion that although propylene glycol may perform some stabilizing function, it does not do so in a way taught by the '249 patent to achieve the same result as taught in the patent.

XI. Other Matters

87. I am being compensated for my time at my customary rate of $500 per hour for consulting, and $750 per hour for time spent giving deposition and trial testimony.

88. I have based my analysis on documents that were available as of the date of this report. I reserve the right to modify and supplement my opinions to reflect any new evidence that may become available after the date hereof.

89. My *curriculum vitae* lists the cases in which I testified as an expert during the past four years.

Dated: 3/14/06

Arthur H. Kibbe

Arthur H. Kibbe